Effectiveness of an additional individualized multi-component complementary medicine treatment on health-related quality of life in breast cancer patients: a pragmatic randomized trial

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CLINICAL TRIAL

Effectiveness of an additional individualized multi-component complementary medicine treatment on health-related quality of life in breast cancer patients: a pragmatic randomized trial

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Abstract The aim of this study was to evaluate the effectiveness of an additional, individualized, multi-component complementary medicine treatment offered to breast cancer patients at the Merano Hospital (South Tyrol) on health-related quality of life compared to patients receiving usual care only. A randomized pragmatic trial with two parallel arms was performed. Women with confirmed diagnoses of breast cancer were randomized (stratified by usual care treatment) to receive individualized complementary medicine (CM group) or usual care alone (usual care group). Both groups were allowed to use conventional treatment for breast cancer. Primary endpoint was the breast cancer-related quality of life FACT-B score at 6 months. For statistical analysis, we used analysis of covariance (with factors treatment, stratum, and baseline FACT-B score) and imputed missing FACT-B scores at 6 months with regression-based multiple imputation. A total of 275 patients were randomized between April 2011 and March 2012 to the CM group ($n = 136$, 56.3 ± 10.9 years of age) or the usual care group ($n = 139$, 56.0 ± 11.0). After 6 months from randomization, adjusted means for health-related quality of life were higher in the CM group (FACT-B score 107.9; 95 % CI 104.1–111.7) compared to the usual care group (102.2; 98.5–105.9) with an adjusted FACT-B score difference between groups of 5.7 (2.6–8.7, $p < 0.001$). Thus, an additional individualized and complex complementary medicine intervention improved quality of life of breast cancer patients compared to usual care alone. Further studies evaluating specific effects of treatment components should follow to optimize the treatment of breast cancer patients.

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Keywords Comparative effectiveness research · Complementary medicine · Pragmatic randomized controlled trial · Breast cancer

Introduction

The demand for complementary medicine (CM) in cancer patients is growing [1]. In Europe, 30–40 % of cancer patients use some form of CM [1, 2]. Women with breast cancer are the largest group [2–4] with an increasing demand [5]. The main reasons for usage are improvement of quality of life, physical and mental well-being, boosting the immune system, and alleviating side effects of the conventional treatments [2, 4, 6–8]. Dietary supplements, herbal medicines, and mind–body techniques are the most frequently used modalities [2–4, 7, 9]. There is a need to evaluate CM especially in breast cancer patients, preferably within randomized trials [10]. However, previous studies have mainly focused on single interventions, although most patients use more than one CM modality [11, 12].

In most medical fields, evidence that directly informs clinical and health policy decision making is needed [13]. Published evidence from clinical trials in oncology often differs from observations made in a usual care patient population [14]. Comparative Effectiveness Research (CER) emphasizes the comparison of different treatment options in usual care settings by including more heterogeneous patients, using less standardized treatment protocols and measuring patient-centered outcomes [15]. The Institute of Medicine in the US mentioned cancer as one priority for CER [16]. A broad spectrum of methods can be applied to CER including randomized trials [17–19]. These so-called "pragmatic trials" play an important role in CER [20] with the advantage that they maintain internal validity deriving from randomization while being designed and implemented to increase external validity. This enables a better assessment of real-world benefits and risks, and the results can guide clinical and health policy decisions [20]. Pragmatic trials do not necessarily have to be blinded or double blinded [10].

In January 2010, the regional public health system in South Tyrol (Italy) established a service for CM at the Merano Hospital planned to run for 2 years, and aiming to improve quality of life in cancer patients and patients with chronic conditions. The present study was initiated by the regional public health system to inform the decision whether or not the service should be maintained after December 2012. Therefore, the primary aim of this study was to evaluate the effectiveness of an additional, individualized, multi-component CM treatment offered at the Merano Hospital compared to usual care only on health-related quality of life in patients with breast cancer.

Materials and methods

Design

Following the recommendations for CER, we conducted a pragmatic randomized trial [19, 20]. Patients were allocated to a group that received a complex individualized CM treatment from the service for CM at the Merano Hospital, Italy, in addition to usual care (CM group) or to a group that received no additional CM treatment (usual care group). The study period per patient was 6 months. The duration of the treatment varied between patients due to the highly individualized treatment, but was terminated after a maximum of 6 months. The patients of the usual care group received no CM treatment at the Merano Hospital during the first 6 months, but to reduce patient selection bias they were offered the respective treatment after the end of the study. The CM therapy within the study was free of charge. Usual care was conducted following oncologic guidelines and after interdisciplinary tumor boards and was covered by the patients' health insurance. The study protocol was approved by the local ethics committee of South Tyrol (statement 10/2011).

Patients

Patients with a diagnosis of breast cancer were recruited between April 2011 and March 2012 in breast cancer centers of Merano, Bressanone, and Bolzano, Italy. After meeting the inclusion criteria and providing written informed consent, they were randomized in a 1:1 ratio and stratified according to the planned usual care treatment during the study period (four strata: chemotherapy, endocrine therapy, chemotherapy and endocrine therapy, neither chemotherapy nor endocrine therapy). The randomization list was generated using the software SAS (SAS Inc., Cary NC, USA) by a statistician not further involved in the study and was embedded in a secure database. None of the study personnel had access to the randomization list before the actual allocation. Screening, randomization, and enrolling of the study participants was done at the onsite study office by a psychologist not involved in the intervention. After registration of the patient details in the database, randomization was performed using a randomization control.

Patients were included if they had a verified diagnosis of breast cancer, were receiving usual care for cancer or related symptoms at the time of the study, and were willing to refrain from CM treatment for 6 months if they were randomized to the usual care group. Exclusion criteria were a CM treatment at the Merano Hospital during the period of 6 months prior to the study, insufficient language ability, and participation in another study.

Interventions

All patients received their usual oncological care from those breast cancer centers they were routinely seeing as part of their cancer treatment. The treatment components, the frequency, and the overall duration of the additional complex and individualized CM treatment of the CM group were highly individualized according to the patient's clinical presentation and her needs and taking into account possible interaction with conventional treatment. Components of the treatments included infusions according to the patient's hemogram and conventional treatment (with ingredients such as alpha factor, high-dosage vitamin C, selenium, carnitine, vitamins), acupuncture (e.g., for treating pain and nausea), hyperthermia, movement therapy (e.g., qigong), enzyme therapy, laser therapy (especially for patients with oral mucositis), mistletoe therapy, orthomolecular therapy, osteopathy, phytotherapy incl. Chinese herbal medicine. Physicians, nurses, and physiotherapists of the CM service conducted the treatments.

Outcome measures

At baseline, patients' socio-demographic as well as cancer-related data were documented. Where available, data were obtained from the hospitals' clinical health records.

The primary outcome parameter was disease-related quality of life assessed with the Functional Assessment of Cancer Therapy-Breast (FACT-B) [21] after 6 months. Secondary outcome parameters were the FACT-B after 3 months, after 3 and 6 months the FACT-General (G) [22] subscales (physical, functional, social, and emotional well-being), the FACT-B subscale Breast, three single items of the FACT-G (pain, sleep, and nausea), fatigue assessed with the FACIT-fatigue scale [23], health-related quality of life assessed with the SF-12 [24], and after 6 months the proportion of responders, relapse-free survival, overall survival, adverse events (AEs), and treatment interactions. AEs were extracted from clinical health records. In the CM group, AEs and possible interactions between therapies were also documented by the CM doctor as well as changes of the CM or conventional treatment due to adverse events.

Patients in the CM group were asked to rate the overall effectiveness and their satisfaction with the CM intervention after 3 and 6 months. Furthermore, at baseline, patients in the CM group decided together with their physicians on up to three treatment goals that were evaluated after 3 months independently by patient and physician and after 6 months by the patient only (goal attainment scaling).

Patients completed paper–pencil questionnaires at baseline, after 3 and after 6 months. The questionnaires were available in German and Italian, the official languages in South Tyrol. The patients completed the questionnaires at home and mailed them back to the study office that was responsible for all data collection. They were reminded by telephone if they failed to send back a questionnaire.

Statistics

Sample size calculation

Assuming an effect size of 0.35 (small to moderate effect) regarding the FACT-B at 6 months, a power of 80 %, and a two-sided t test with an alpha of 0.05, 130 patients have to be included in each group. Allowing for dropouts, 280 patients were to be included in the study.

Analyses

Data analyses followed a predefined and signed statistical analysis plan (SAP) agreed upon by the Steering Committee. Socio-demographic and disease-related characteristics at baseline are presented as means with standard deviation for continuous data and frequencies with percentages for categorical data. The primary analysis of the primary endpoint (FACT-B score after 6 months) was performed by analysis of covariance (ANCOVA) including the treatment and stratum variables as fixed effects, and the baseline FACT-B score as covariate. Results for the treatment effect are presented as adjusted means for each treatment group and for the group difference, with 95 % confidence intervals and the corresponding p value. The p value was two-sided and the type I error level was set at 0.05. This analysis was performed on the intention-to-treat (ITT) population with multiple imputation of missing FACT-B scores after 6 months. Multiple imputation was performed using SAS PROC MI and PROC MIANALYZE (SAS for Windows Version 9.3, SAS Institute Inc., Cary, NC USA) with a Markov Chain Monte Carlo (MCMC) method stratified by treatment group. Five thousand iterations were used before the first imputation and 5,000 iterations were performed between successive imputations. The number of imputations was set to 100. The selection of imputation variables and the primary analyses of the primary endpoint were performed blinded to treatment allocation. All further analyses (secondary outcomes, further time points, subgroups, and sensitivity analyses) were performed without missing imputations and were considered exploratory.

Sensitivity analyses for the primary endpoint included the same ANCOVA model without imputation of missing value and using the last observed FACT-B value for imputation (LOCF). In addition, the primary analysis model was extended to adjust for further characteristics at baseline (education, income, previous CM use, attitude toward CM).

Secondary endpoints were analyzed using ANCOVA by adjusting for baseline values (where available) and randomization stratum for continuous variables. For binary endpoint outcomes (e.g., proportion of responders, defined by a FACT-

B score improved by ≥7 points), logistic regression adjusted for baseline values and randomization stratum was used. Effect size for the primary endpoint (adjusted for baseline value and stratum) was calculated post hoc (not described in the SAP). Adverse events will be presented descriptively presenting number and percentage of patients with adverse events (compared between treatment groups by Chi-square test).

Predefined subgroup analyses were planned using models as described above with interaction terms between treatment group and subgroup regarding the following baseline characteristics: randomization stratum, time since first diagnosis of breast cancer, time since last recurrence, cancer stage, tumor grade, number of recurrences, age groups, and native language (German, Italian).

For the safety analysis, AEs were classified according to the Common Terminology Criteria for Adverse Events established by the US National Cancer Institute [25]. An independent samples *t* test was conducted to compare the mean number of AEs documented in the patient's record between the two groups. The frequency distributions of the different AE categories in the two groups were compared via Chi-square test. The mean number of AEs that was only documented by the CM doctor, and the frequency of different AE categories of these AEs also was computed.

Results

Between April 2011 and March 2012, a total of 442 patients were screened for eligibility to participate in the study (Fig. 1). A total of 275 patients were randomized, 136 to the CM group, 139 to the usual care group. Data for the main effectiveness analysis were available for 234 patients (85 %, Fig. 1). Baseline characteristics and medical history were mostly comparable between both study groups (Table 1). The overall attitude toward CM was very

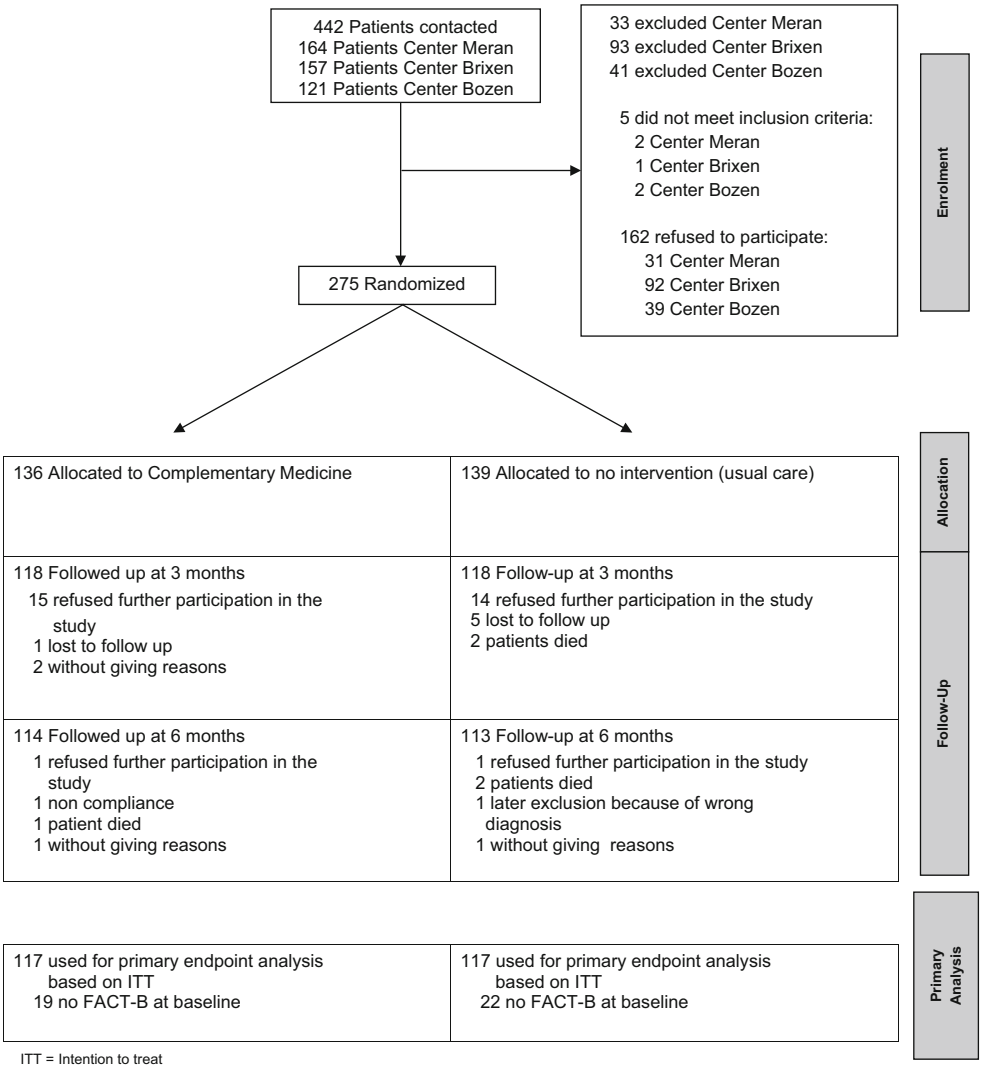

Fig. 1 CONSORT flow chart for the study

Table 1 Baseline characteristics and medical history

	Complementary medicine group ($n = 136$) Mean ± SD/n (%)	Usual care group ($n = 139$) Mean ± SD/n (%)
Age (years)	56.3 ± 10.9	56.0 ± 11.0
School education		
>10 years of schooling	78 (60.5 %)	76 (58.5 %)
Primary language		
German	96 (70.6 %)	97 (69.8 %)
Italian	40 (29.4 %)	42 (30.2 %)
Family income (€/months)		
<2000 Euro	71 (71.7 %)	51 (55.4 %)
≥2000 Euro	28 (28.3 %)	41 (44.6 %)
Breast cancer center		
Bozen	35 (25.7 %)	46 (33.1 %)
Brixen	33 (24.3 %)	32 (23.0 %)
Meran	68 (50.0 %)	61 (43.9 %)
Years since first diagnosis	3.4 (3.2)	3.1 (3.2)
Tumor type		
Carcinoma in situ	32 (23.9 %)	34 (25.2 %)
Invasive ductal carcinoma	104 (77.6 %)	104 (77.0 %)
Invasive lobular carcinoma	19 (14.2 %)	24 (17.8 %)
Inflammatory breast cancer	0 (0 %)	0 (0 %)
Tumor stage (first diagnosis or last relapse)		
Stage 0	7 (5.4 %)	5 (3.8 %)
Stage I	57 (43.8 %)	51 (38.6 %)
Stage II	47 (36.2 %)	59 (44.7 %)
Stage III	16 (12.3 %)	9 (6.8 %)
Stage IV	3 (2.3 %)	8 (6.1 %)
Tumor grading		
G1	13 (10.1 %)	17 (13.4 %)
G2	58 (45.0 %)	56 (44.1 %)
G3	58 (45.0 %)	54 (42.5 %)
Relaps		
None	126 (92.6 %)	133 (95.7 %)
1	8 (5.9 %)	6 (4.3 %)
≥2	2 (1.5 %)	0 (0 %)
Menopause		
Pre-/perimenopausal	51 (39.8 %)	60 (46.9 %)
Postmenopausal	77 (60.2 %)	68 (53.1 %)
Previous surgery		
Breast conserving (lumpectomy or Quadrantectomy)	112 (78.0 %)	104 (79.4 %)
Mastectomy	34 (25.8 %)	34 (26.0 %)
Undefined surgery	2 (1.5 %)	3 (2.3 %)
Previous radiation therapy		
External radiation	83 (66.9 %)	87 (73.1 %)
Brachytherapy	1 (0.8 %)	1 (0.8 %)
Undefined radiation	6 (4.8 %)	4 (3.4 %)
Previous chemotherapy	62 (50.8 %)	64 (53.3 %)
Previous hormone therapy		
Tamoxifen or fulvestarant	13 (11.2 %)	8 (7.0 %)

Table 1 continued

	Complementary medicine group ($n = 136$) Mean ± SD/n (%)	Usual care group ($n = 139$) Mean ± SD/n (%)
AIs	8 (6.9 %)	7 (6.1 %)
LHRH analog	7 (6.0 %)	2 (1.7 %)
Previous antibody therapy	10 (8.5 %)	6 (5.6 %)
Previous bisphosphonate therapy	6 (5.2 %)	11 (10.1 %)
Stratification group		
Chemotherapy	15 (11.0 %)	15 (10.8 %)
Hormones	80 (58.8 %)	79 (56.8 %)
Chemotherapy + hormones	1 (0.7 %)	3 (2.2 %)
No chemotherapy + no hormones	40 (29.4 %)	42 (30.2 %)
Previous use of complementary medicine (most frequent)		
Any	30 (22.9 %)	45 (34.4 %)
Acupuncture	11 (8.4 %)	11 (8.6 %)
Bach flowers	6 (4.6 %)	7 (5.5 %)
Homeopathy	12 (9.2 %)	15 (11.7 %)
Meditation	2 (1.5 %)	6 (4.7 %)
Mistletoe	5 (3.8 %)	8 (6.3 %)
Other phytomedicine	6 (4.6 %)	4 (3.1 %)
Qigong/Tai Chi/Yoga	3 (2.7 %)	9 (7.0 %)
Other	17 (13.0 %)	30 (23.4 %)
Attitudes toward complementary medicine		
I do not believe that it works	3 (2.3 %)	0 (0 %)
Only in addition to conventional medicine	67 (52.3 %)	73 (57.0 %)
Could be a good alternative to conventional medicine	57 (44.5 %)	49 (38.3 %)
Overall more effective than conventional medicine	1 (0.8 %)	6 (4.7 %)
FACT-B	98.3 ± 19.2	100.7 ± 19.5
FACT-G subscales		
Physical well-being	20.9 ± 5.7	21.5 ± 5.3
Social and family well-being	19.3 ± 5.7	19.5 ± 5.8
Emotional well-being	18.1 ± 4.0	17.8 ± 4.1
Functional well-being	17.1 ± 5.7	18.2 ± 5.1
FACT-G single items		
Pain	1.3 ± 1.2	1.2 ± 1.2
Sleep	1.9 ± 1.2	2.1 ± 1.3
Nausea	0.5 ± 0.9	0.4 ± 0.8
FACIT-fatigue scale	36.3 ± 11.0	36.5 ± 11.2
Quality of life (SF-12)		
Mental component scale	44.0 ± 10.2	44.8 ± 11.8
Physical component scale	43.9 ± 9.7	44.0 ± 10.4

SD Standard deviation, *FACT-B* Functional Assessment of Cancer Therapy-Breast, *FACT-G* Functional Assessment of Cancer Therapy General, *FACIT* Functional Assessment of Chronic Illness Therapy

positive, although only 23 % of the patients in the CM group and 34 % of patients in the usual care group had used CM before (Table 1).

During the study, patients in the CM group were individually treated (Table 2). The conventional oncological treatment was comparable in both groups and patients of both groups used CM outside the service of the Merano Hospital (Table 3).

In the primary analysis after 6 months, adjusted means for health-related quality of life were higher in the CM group (FACT-B score 107.9; 95 % CI 104.1–111.7) compared to the usual care group (102.2; 98.5–105.9) with an

Table 2 Treatment in the complementary medicine group (study intervention)

	Complementary medicine Mean ± SD/*n* (%)
Individualized study intervention	
Acupuncture	66 (48.5 %)
Number of treatments	6.9 ± 3.9
Dietary advice	20 (14.7 %)
Healing touch	1 (0.7 %)
Homeopathy	62 (45.6 %)
Hyperthermia	3 (2.2 %)
Infusions	59 (43.4 %)
Number of treatments	9.25 ± 6.55
Laser therapy	17 (12.5 %)
Number of treatments	4.00 ± 2.31
Lymphatic drainage	4 (2.9 %)
Magnet field therapy	19 (14.0 %)
Number of treatments	7.6 ± 6.1
Manual therapy	2 (1.5 %)
Neural therapy	8 (5.9 %)
Orthomolecular therapy	66 (48.5 %)
Osteopathy	26 (19.1 %)
Number of treatments	5.7 ± 2.7
Phytotherapy	35 (25.7 %)
Shiatsu	1 (0.7 %)

adjusted FACT-B score difference between groups of 5.7 (2.6–8.7, $p < 0.001$).

This improvement was robust in the sensitivity analyses for missing data and the extended model adjusting for further characteristics at baseline (data not shown). Responder rates were higher in the CM group compared to the usual care group (adjusted odds ratio 0.4, 95 % CI 0.2–0.7, $p = 0.003$). The adjusted effect size for the difference between groups according to Cohen's d was 0.53. No subgroup showed a significant effect modifying influence regarding FACT-B at 6 months.

For most secondary outcomes, the results of the patients in the CM group were superior to those in the usual care group (Table 4). Three patients died during the study (1 in the CM group and 2 in the usual care group, Fig. 1), and one relapse occurred in the usual care group. Before the intervention, patients in the CM group defined with their physicians on average 2.6 ± 0.7 treatment goals and assessed those after 3 and 6 months. (Table 5). The patients were mostly satisfied with the CM treatment and found it effective (Table 5).

Safety

The mean number of AEs documented in the patient's records was 0.52 (SD = 1.14) in the CM group and 0.64 (2.10) in the usual care group ($p = 0.56$). Most AEs belonged to the spectrum of musculoskeletal and connective tissue disorders (22.5 %), gastrointestinal disorders (13.1 %), and general disorders (13.1 %), with no significant difference between groups ($p = 0.41$, Table 6). The additional documentation for the CM patients resulted in a mean number of 2.92 (SD = 1.63) AEs per patient. Most of these AEs were musculoskeletal and connective tissue disorders (24.4 %), followed by psychiatric disorders (20.4 %), and general disorders (16.1 %) (Table 6). For two patients in the CM group, the CM treatment was changed due to AEs, and for two patients in the usual care group, the conventional treatment was changed due to AEs.

Discussion

Breast cancer patients treated with an individualized multicomponent CM treatment at the Merano Hospital showed significant improvements in disease-specific quality of life and fatigue compared with patients who received standard care alone.

To our knowledge, the present study is the first randomized trial in breast cancer patients evaluating the effectiveness of a complex and individualized CM intervention in a usual care setting. We used the framework of CER and designed a pragmatic trial [19] that allowed us to answer the question if the CM service implemented by the regional public health system had a positive effect on quality of life of cancer patients and should be maintained.

We focused on breast cancer patients because they made up the largest group using the respective service. Thus the study results cannot be transferred to other patients. Furthermore, the results relate to the specific interventions and setting of the Hospital Merano and cannot be transferred to other interventions and settings.

Advantages of our approach to provide useful information for decision making regarding continuation of the service included an outcome measure that was recommended for incorporating patient-reported outcomes into CER [26], a setting and intervention that reflected usual care, broad eligibility criteria, and the participation of all existing breast cancer centers in the region.

Clearly, this kind of approach also has methodological limitations. Neither physicians nor patients were blinded to treatment. To minimize social acceptability bias, all questionnaires were sent directly from and to the psychologist who was not further involved in the patients' treatment. However, bias regarding the patient-reported main outcome resulting from non-blinding to the intervention cannot be ruled out. Also, there might be bias attributable to participating physicians' and practitioners' positive attitudes about CM, their affiliation with the governmental

Table 3 Concomitant treatments in both groups

	Complementary medicine *n* (%)		Usual care *n* (%)	
	3 months	6 months	3 months	6 months
Complementary medicine outside the study				
Any	11 (9.6 %)	19 (16.8 %)	27 (23.7 %)	25 (22.5 %)
Acupuncture	4 (3.5 %)	4 (3.5 %)	5 (4.5 %)	2 (1.8 %)
Bach flowers	1 (0.9 %)	1 (0.9 %)	2 (1.8 %)	2 (1.8 %)
Homeopathy	8 (7.0 %)	7 (6.2 %)	10 (8.9 %)	6 (5.5 %)
Meditation	1 (0.9 %)	4 (3.5 %)	4 (3.6 %)	5 (4.6 %)
Mistletoe	3 (2.6 %)	4 (3.5 %)	3 (2.7 %)	5 (4.6 %)
Other phytomedicine	1 (0.9 %)	2 (1.8 %)	4 (3.6 %)	2 (1.8 %)
Qigong/Tai Chi/Yoga	2 (1.8 %)	5 (4.4 %)	5 (4.5 %)	7 (6.4 %)
Other	9 (7.8 %)	14 (12.6 %)	19 (16.9 %)	17 (15.6 %)
Usual care cancer treatment				
Surgery				
Breast conserving surgery (Lumpectomy or Quadrantectomy)	0 (0 %)		0 (0 %)	
Mastectomy	1 (0.8 %)		1 (0.8 %)	
Undefined surgery	1 (0.8 %)		1 (0.8 %)	
Radiation therapy				
External	10 (8.1 %)		7 (5.9 %)	
Brachytherapie	0 (0 %)		0 (0 %)	
Undefined	1 (0.8 %)		2 (1.7 %)	
Chemotherapy	8 (6.6 %)		10 (8.3 %)	
Hormone therapy				
Tamoxifen o. fulvestarant	27 (23.5 %)		25 (21.7 %)	
AIs	51 (44.3 %)		51 (44.3 %)	
LHRH analog	18 (15.7 %)		17 (14.8 %)	
Antibody therapy	6 (5.1 %)		7 (6.5 %)	
Bisphosphonates	3 (2.6 %)		1 (0.9 %)	
Patients in hospital (patient reported)	10 (9.0 %)		9 (8.5 %)	

project, and possible personal or financial interests in producing results in favor of CM. Our inclusion criteria were broad, which resulted in a heterogeneous patient sample and diagnostic misclassification can happen in this type of study. We had one patient claiming to have breast cancer, who was randomized to the usual care group. When comparing her interview data with the clinical health records, the diagnosis could not be confirmed. Using a more conservative approach by strictly following ITT analyses, we included her in the primary analysis, but performed an additional sensitivity analysis without this patient, which did not change the results. That not all patients received the treatment that was planned at baseline cannot be avoided in a study that reflects usual care.

Finally, our patients had a highly positive attitude toward CM treatment. However, adjusting for attitude in a sensitivity analysis did not change the main outcome. Although the issues mentioned above are considered limitations from an experimental perspective, the study design was chosen to reflect general medical practice as closely as possible. A more experimental approach would not have been suitable to answer the study question.

It is important to highlight that this study does not provide any information on the effectiveness of the single CM modalities used within the complex intervention. Further studies separating different modalities, perhaps multi-armed studies would be needed to generate evidence on this question. In fact, there are studies on single complementary treatment modalities for breast cancer patients, e.g., on acupuncture used for the alleviation of symptoms caused by aromatase inhibitors [27–29], or for treating cancer-related fatigue [30, 31].

Furthermore, this study cannot answer the question of how much of the observed effects can be attributed to non-specific effects. Based on evidence that some of the interventions have relevant non-specific effects (i.e. acupuncture) [32], those also contribute to our results. The numbers of AEs were low and did not differ in both groups.

Table 4 Primary and secondary outcomes after 3 and 6 months (from analysis of covariance adjusted for randomization stratum and baseline value)

	3 months				6 months			
	Complementary medicine mean (95 % CI)	Usual care mean (95 % CI)	Usual care versus complementary medicine Δ (95 % CI)	*p* value	Complementary medicine mean (95 % CI)	Usual care mean (95 % CI)	Usual care versus complementary medicine Δ (95 % CI)	*p* value
FACT-B[a]	107.1 (103.6; 110.7)	101.0 (97.5; 104.5)	6.1 (3.3; 9.0)	<0.001	107.9[b] (104.1; 111.7)	102.2[b] (98.5; 105.9)	5.7[b] (2.6; 8.7)	<0.001
FACT-G subscales[a]								
Physical well-being	23.5 (22.5; 24.6)	21.2 (20.1; 22.3)	2.3 (1.5; 3.2)	<0.001	24.3 (23.1; 25.5)	22.3 (21.1; 23.5)	2.0 (1.0; 3.0)	<0.001
Social well-being	19.8 (18.6; 20.9)	19.4 (18.2; 20.5)	0.4 (−0.5; 1.3)	0.38	19.8 (18.4; 21.2)	19.7 (18.4; 21.0)	0.1 (−0.8; 1.0)	0.8
Emotional well-being	19.0 (18.1; 19.9)	18.6 (17.7; 19.5)	0.4 (−0.3; 1.1)	0.24	19.3 (18.5; 20.1)	18.4 (17.6; 19.2)	0.9 (0.3; 1.5)	0.005
Functional well-being	18.7 (17.6; 19.9)	17.8 (16.6; 18.9)	1.0 (0.1; 1.9)	0.03	19.1 (18.0; 20.3)	17.6 (16.5; 18.8)	1.5 (0.6; 2.4)	0.001
FACT-G single items[a]								
Pain	0.9 (0.6; 1.2)	1.13 (0.8; 1.4)	−0.2 (−0.4; −0.0)	0.04	0.9 (0.6; 1.2)	1.2 (0.9; 1.5)	−0.3 (−0.5; −0.0)	0.04
Sleep	2.1 (1.8; 2.3)	1.93 (1.6; 2.2)	0.1 (−0.1; 0.3)	0.29	2.2 (1.9; 2.5)	2.0 (1.8; 2.3)	0.2 (−0.1; 0.4)	0.2
Nausea	0.2 (−0.0; 0.3)	0.26 (0.1; 0.4)	−0.1 (−0.2; 0.0)	0.07	0.1 (−0.1; 0.3)	0.2 (0.0; 0.4)	−0.1 −0.3; 0.0)	0.1
FACIT-Fatigue Scale[a]	38.9 (36.7; 41.1)	36.0 (33.8; 38.1)	2.9 (1.2; 4.6)	<0.001	41.2 (38.8; 43.7)	37.9 (35.5; 40.3)	3.4 (1.5; 5.3)	<0.001
Quality of life (SF-12)[a]								
Mental component scale	50.4 (47.6; 53.2)	47.2 (44.5; 49. 9)	3.2 (0.9; 5.4)	0.006	54.3 (49.8; 58.9)	53.2 (48.8; 57.6)	1.2 (−1.3; 3.6)	0.4
Physical component scale	44.7 (42.6; 46.9)	42.1 (40.0; 44.2)	2.6 (0.9; 4.4)	0.003	44.2 (40.5; 48.0)	40.8 (37.2; 44.4)	3.4 (1.4; 5.5)	0.001

FACT-B Functional Assessment of Cancer Therapy-Breast, *FACT-G* Functional Assessment of Cancer Therapy-General, *FACIT* Functional Assessment of Chronic Illness Therapy

[a] Higher values indicate higher well-being

[b] Primary outcome

Table 5 Complementary medicine group: patients overall rating of effectiveness, satisfaction, and goal attainment scaling at 3 and 6 months

Variable	3 months		6 months
	Patient	Physician	Patient
Goal attainment scaling[a] (mean ± SD)			
Goal 1	0.4 ± 1.0	0.4 ± 0.8	0.3 ± 1.0
Goal 2	0.3 ± 1.0	0.2 ± 0.8	0.4 ± 1.0
Goal 3	0.1 ± 1.0	0.1 ± 0.8	0.2 ± 1.0
Average of goal-1-3	0.3 ± 1.0	0.3 ± 0.8	0.3 ± 1.0
Rating of effectiveness			
Very effective	18 (15.3 %)		23 (20.2 %)
Effective	88 (74.6 %)		83 (72.8 %)
Small effect	12 (10.2 %)		7 (6.1 %)
No effect	0 (0 %)		1 (0.9 %)
Satisfaction with CM treatment			
Very satisfied	50 (42.7 %)		38 (33.3 %)
Satisfied	58 (49.6 %)		68 (59.6 %)
Not very satisfied	9 (7.7 %)		7 (6.1 %)
Not satisfied	0 (0 %)		1 (0.9 %)

[a] −2 points worse than expected, −1 no change, 0 aim reached, 1 better than expected, 2 much better than expected

Table 6 Number of adverse events in both groups

	CM group *n* (%)	Usual care group *n* (%)	Total *n* (%)
AEs documented in clinical records			
Blood and lymphatic system disorders	1 (1.4 %)	3 (3.4 %)	4 (2.5 %)
Ear and labyrinth disorders	1 (1.4 %)	1 (1.1 %)	2 (1.2 %)
Gastrointestinal disorders	11 (15.5 %)	10 (11.2 %)	21 (13.1 %)
General disorders and administration site conditions	8 (11.3 %)	13 (14.6 %)	21 (13.1 %)
Hepatobiliary disorders	1 (1.4 %)	0 (0.0 %)	1 (0.6 %)
Immune system disorders	1 (1.4 %)	0 (0.0 %)	1 (0.6 %)
Infections and infestations	6 (8.5 %)	2 (2.2 %)	8 (5.0 %)
Injury, poisoning and procedural complications	2 (2.8 %)	0 (0.0 %)	2 (1.2 %)
Investigations	1 (1.4 %)	2 (2.2 %)	3 (1.9 %)
Metabolisms and nutrition disorders	0 (0.0 %)	1 (1.1 %)	1 (0.6 %)
Musculoskeletal and connective tissue disorders	16 (22.5 %)	20 (22.5 %)	36 (22.5 %)
Nervous system disorders	8 (11.3 %)	6 (6.7 %)	14 (8.8 %)
Psychiatric disorders	3 (4.2 %)	12 (13.5 %)	15 (9.4 %)
Renal and urinary disorders	0 (0.0 %)	1 (1.1 %)	1 (0.6 %)
Reproductive system and breast disorders	2 (2.8 %)	5 (5.6 %)	7 (4.4 %)
Respiratory thoracic and mediastinal disorders	1 (1.4 %)	0 (0.0 %)	1 (0.6 %)
Skin and subcutaneous tissue disorders	5 (7.0 %)	6 (6.7 %)	11 (6.9 %)
Vascular disorders	4 (5.6 %)	6 (6.7 %)	10 (6.2 %)
No code available	0 (0.0 %)	1 (1.1 %)	1 (0.6 %)
Total	71 (100.0 %)	89 (100.0 %)	160 (100.0 %)
AEs documented by CM doctor			
Ear and labyrinth disorders	8 (2.0)		
Endocrine disorders	1 (0.3)		
Eye disorders	4 (1.0)		
Gastrointestinal disorders	31 (7.8)		
General disorders and administration site conditions	64 (16.1)		
Immune system disorders	5 (1.3)		
Infections and infestations	6 (1.5)		
Investigations	3 (0.8)		
Metabolisms and nutrition disorders	1 (0.3)		
Musculoskeletal and connective tissue disorders	97 (24.4)		
Nervous system disorders	25 (6.3)		
Psychiatric disorders	81 (20.4)		
Reproductive system and breast disorders	6 (1.5)		
Respiratory thoracic and mediastinal disorders	11 (2.8)		
Skin and subcutaneous tissue disorders	14 (3.5)		
Vascular disorders	34 (8.6)		
No code available	6 (1.5)		
Total	397 (100)		

In usual care, physicians ask their patients less detailed questions about AEs than in clinical trials and even if patients report them, they might not always be documented [33]. In the CM group, the doctors asked explicitly for AEs, resulting in additionally documented AEs, especially psychiatric disorders including anxiety, worries, sleeping problems, or restlessness. This might be explained by the holistic approach of CM doctors asking for both mind and body aspects.

It is difficult to compare our study with other studies because previous studies addressed mainly single CM modalities, for example, yoga [34] or specific intervention programs such as mind–body medicine [35, 36]. There are only few studies that address the topic of complex individualized CM interventions in cancer patients in usual care setting, and none of them used a randomized design [3, 37, 38].

Conclusion

The additional individualized and complex CM intervention offered by the Hospital Merano was more effective in improving quality of life compared to no additional CM intervention in breast cancer patients. Further studies evaluating the effectiveness, efficacy, and safety of treatment components should follow.

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